THE BIOLOGISTS -- Bello, Fullen (Gold)
(1st draft) 3/31/60 rh

The human mind cannot grasp, in any profound and meaningful sense, the incredible richness of the life now existing on the face of the earth. It covers every inch of the earth's surface, suffuses every drop of water, and fills the air we breathe. Neither the polar snows nor the tropical desert sands nor the ocean deeps are truly sterile. Life is everywhere. And what we see is barely a token of all the life that has come and gone, aeon after aeon after aeon. Where single-celled life leaves off, the information-bearing viruses take over, dependent on living cells for their propagation, and intervening in the life of bacteria, plants, animals, and men in a thousand complex ways, only now being revealed and understood.

The Greeks, who had so many profound intuitions about the inanimate world, stood in awe of the animate, scarcely guessing that the two were one and inseparable. When experimental science as we know it was born at the time of Galileo, the study of life lagged far behind, restrained in part by dogmatic teachings, and more powerfully restrained by man's inability to order his thoughts effectively in the presence of life's diversity, fecundity, and mystery. Scant wonder that biology, struggling to emerge in the

seventeenth, eighteenth, and nineteenth centuries, was plagued and crippled by notions of "vitalism." The common-sense distinction between life and non-life is so deep and overpowering that even modern biologists have trouble excluding vitalistic notions from influencing their quest for knowledge. The great uproar that greeted Darwin's ideas barely one hundred years ago attest to the deep-seated resistance among men toward being made one with all nature. While Darwin's views may seem to have prevailed, their victory is every day repudiated by the news from towns and villages where skin color is still deemed important.

For all these and perhaps other reasons, biology has had trouble, until recently, in attracting the best and most creative minds. Men, it seems reasonable to believe, prefer problems which they may hope to solve in a lifetime. Moreover, scientists, as a special class of men, are partial to solutions that are rigorous, mathematically precise, and of broad generality. The problems of biology are so complex and fractious that they must have seemed completely frustrating to any bright young man impatient to come quickly to grips with "truth." In physics and chemistry it was evidently possible for gifted people to have fruitful hunches and intuitions. In biology, by contrast, human intuitions have been invariably weak and almost always wrong.

As recently as 1900 the great majority of biologists could scarcely be called scientists at all. "Most nineteenth

century biologists," says one modern biologist, "were natural history people. They used ordinary powers of perception only a few orders more acute than hunters and fishermen." Today, all is changed. Biology is no longer the stepchild among sciences. It competes vigorously with the physical sciences for the keenest young minds, and it is generously if not bountifully supported by the federal government, with lesser but still important funds from private sources.

The most striking aspect of present-day biology, however, is the almost universal belief that it has moved to the center of the scientific stage, and that it is on the verge of momentous and thrilling discoveries. These discoveries, already becoming visible, should clarify some of the most profound problems of life: how the whole "blueprint" for a bacterium or a man is "coded" in the molecular structure of its genes, and how a single fertilized cell is flawlessly guided through cell division after cell division until it emerges as a fully integrated plant or animal consisting of billions or trillions of smoothly functioning and cooperating cells. The problem of the origin of life, long believed hopelessly insoluble, is under vigorous attack and if earth-bound conjecture and experiment should prove inadequate, there is a good chance that exploration of the moon and planets will provide the clues needed for successful theory.

Biology's search for unity

There is scarcely any doubt among biologists that once

they have gained fundamental understanding of the crucial life processes, practical applications will irresistibly follow. It takes no great act of prophecy to suggest what some of these applications may be, but whether they will come in twenty years or two hundred is utterly unpredictable. The first beneficiary of new biological knowledge will, as usual, be medicine. The disease that seems to arise most directly from a fundamental aberration of cells is, of course, cancer. It is a disease, or group of diseases, that seem to involve a flaw in genetic transmission of "correct" cell behavior. Cancer cells fail to differentiate properly and thus grow without restraint. Other ailments like coronary disease and mental illness seem to contain strong hereditary components and may be subject to attack at the primary genetic level. Conceivably if a genetic flaw is involved, it can be corrected in some fashion not yet evident.

Beyond treatment of illness, biology will surely present man, sooner or later, with the means of altering, and, by some definition, "improving" his innate biological makeup. The social problems that would flow from such biological mastery stagger comprehension. Who would know how to prepare man to deal with the power to raise his intelligence, to double his life span, or to alter his complexion and physical appearance? At the moment this mastery may seem so remote as to be scarcely worth worrying about. But that biology will present society with vexatious problems of some sort, probably before the end of the century, is, to biologists, a foregone conclusion.

In the account that follows, no attempt will be made to present all the high points of modern biology or to present all of its leading contributors. The attempt would be futile. Biology, historically, has been more fragmented than most sciences. Its major experimental divisions include cytology (the study of cells), embryology (the study of growth and development), physiology (the study of the functioning organism), ecology (the study of organisms in their natural environment), plus such specialties as entomology, bacteriology, virology. A recently-named newcomer is psychobiology, the study of innate biological behavior. Operating in all these separate compartments are the biochemists whose studies have provided one of the strong and shining sinews tying together the artificially chopped-up body of biology. The other great unifying sinew that has emerged in this century, timidly at first and now more boldly, is genetics -- the study of how hereditary characters are transmitted from generation to generation. It is these characters, ultimately, that have both emerged from and shaped evolution. And one way or another genetics, when understood in molecular detail, should answer most of the crucial questions about the growth, development, and "psychobiology" of the total organism, from amoeba to man in all his glory. There are, to be sure, biologists who vigorously deny that genetics holds the key to all these deep and diverse problems. But at the moment they are in the minority and it is up to the geneticists to deliver on their audacious promises.

It is significant that in the survey that FORTUNE made to select outstanding American biologists for recognition in this article, the voting ran heavily to geneticists. In fact, of the eleven men whose pictures appear on these pages, nine may be regarded as geneticists, and the other two are biochemists concerned with the immediate consequences of genetics. In order of ~~age~~ youth?, the eleven are: Herman J. Muller, Alfred H. Sturtevant, Sewall Wright, Fritz Lipmann, George W. Beadle, Max Delbrück, Alfred D. Hershey, Arthur Kornberg, Seymour Benzer, Joshua Lederberg, and James D. Watson. As in previous selections in this series, many distinguished names are regrettably omitted.

Since genetics has been the American specialty for sixty years, it is probably safe to say that the eleven scientists selected have no superiors anywhere in the world, and, age for age, very few peers. Of the eleven, all but two (?) are American born and educated. Among them they have collected five Nobel Prizes. Two earned their Ph.D.'s in physics, and became biologists and geneticists by self-tutoring.

Thunder in the "fly room"

Our story begins in 1909 at Columbia University. Outside the university, swarming around the garbage cans in every alley, fruit flies, technically known as drosophila melanogaster, were living luxuriously off decaying vegetable matter, innocent of the tremendous contribution they were soon to make to human

knowledge. Inside the university, professor E. B. Wilson, pioneer embryologist and cytologist, head of the biology department, was telling a sophomore class about the exciting rediscovery, in 1900, of the sweet pea experiments performed in the early 1860's by the Austrian monk, Gregor Mendel. The experiments, printed in an obscure journal and "lost" for thirty-five years, showed how various characteristics of the sweet pea were passed on from generation to generation. They showed, for example, how the hereditary factor for red flowers is dominant over white, so that in any cross between a pure red strain and a pure white strain, all immediate descendents are red. In later generations, however, the recessive white factor will systematically reappear, with a certain probability, in individuals inheriting two of the recessive factors.

One of the students listening to Wilson (innocently as a fruit fly) was Herman J. Muller, only child of one of New York's leading fabricators of ornamental iron work. In New York's Morris High School, before entering Columbia, young Muller and a friend, Edgar Altenburg, had founded what may have been the first high school science club in America. They had excluded biology from discussion in the club because it was too unscientific. But listening now to Wilson, one of the leading biologists of his day, Muller -- and Altenburg, who was in the same class -- had a thrilling glimpse of how biology could be transformed into a science as analytical and as precise as the physical sciences. After school hours the two boys pored

over one of the remarkable books of its day, Recent Progress in Heredity, Variation, and Evolution, written by an Englishman, R. H. Lock[e]? It was not to be the first time that students were to be charmed into entering biology by a gifted teacher and a book.

The same year, 1909, Wilson's [act. 43 junior] associate in the biology department, [Professor] Thomas Hunt Morgan, collected some of the local fruit flies and tried to see if he could cause mutations by exposing them to chemicals, radium, and x-rays. 21 Morgan, (related both to General John Hunt Morgan of "Morgan's Raiders," and to J. P. Morgan, the financier), was already a famous biologist in his forties when he began his fruit-fly experiments. He soon found that mutations indeed occurred, but they seemed to occur about as often whether he tried to induce them or not. (The reasons for Morgan's lack of success will become clear later.) Morgan's "fly room," jammed with milk bottles containing fly colonies, became famous among the biology students, which included not only Muller and Altenburg, but two others destined for greatness: Alfred H. Sturtevant and Calvin B. Bridges. Sturtevant and Bridges showed such interest and promise that Morgan gave them desks in his fly room while they were still undergraduates.

Only a few times in a century will fate bring together such an inspired scientist and teacher, such gifted students, and a research venture so ripe for exploitation. Though the effort to induce mutations failed, Morgan and his young associates switched to other problems and in astonishingly short order laid down almost

all the basic concepts upon which genetics has been building ever since. Morgan's great initial discovery was that certain genetic features, for example a white eye, were sex-linked, meaning that the features were commonly transmitted only to ♂ offspring [of one sex.] (In humans, such defects as hemophilia and color-blindness are sex-linked, being many times more common in men than in women.) Almost immediately, however, Morgan was puzzled by some anomalous cases of inheritance: sex-linked features sometimes appeared where prevailing theory said they should not.

Morgan was able to show by 1910 that one element of the old theory was wrong. It held that the thread-like chromosomes which carry hereditary "factors" (not called "genes" until 1911), were fairly rugged bits of matter, unlikely to break or alter except by mutation. Morgan could explain his results only by supposing that breaking actually occurred and that there was some sort of exchange of parts between chromosomes. This fruitful concept became known as "crossing-over." From nature's point of view, not to say man's, "crossing-over" is one of the earth-shaking glories of bisexual reproduction. Together with mutation, it is one of the great powerhouses of evolution. If the forty-six chromosomes in man -- twenty-three from each parent -- did not cross over, but were simply "dealt" randomly into two piles of twenty-three chromosomes each, at the time that the gonads produce germ cells (i.e., sperm or egg cells), there would be about one chance in eight million for all the

chromosomes "dealt" into one germ cell to come entirely from one of the grandparents, instead of representing a mixture of chromosomes from both. Thus, once in every eight million births -- not a very high number, genetically speaking -- the entire family line of one grandparent would be abruptly and capriciously extinguished. In a simple creature like the fruit fly with only eight chromosomes, this familial extinction would occur once every sixteen (?) births.

Almost as soon as Morgan had made these findings, his young associates announced major discoveries of their own:

Sturtevant, in 1913, while still a graduate student, published the first "map" showing the location along the chromosome of genes associated with various inherited characteristics of the fruit fly. To prepare the "map" he studied the frequency with which chromosomes "cross-over" and recombine. Gene location can be deduced from the fact that two genes lying very near together will seldom be separated when a chromosome breaks; genes far apart, on the other hand, will almost always be separated by any break in the chromosome chain. Before Sturtevant's work it was possible to hold the most bizarre notions of how genes might be scattered about inside a chromosome, or even elsewhere in a cell. Sturtevant showed, to the surprise of many, that they were strung together in simple linear fashion.

Bridges, also in 1913, noted that in the special type of cell divisions (meiosis) leading up to the formation of the sperm or egg, the number of chromosomes was not always divided exactly in half, but that the process sometimes went awry, causing the egg (or sperm) to contain one chromosome too many or one chromosome too few. This genetic error, called "non-disjunction," gives rise to flies with defective sexual characteristics, as a result of which they are usually sterile. Just last year, non-disjunction was found to be the cause of genital abnormalities in a few rare humans. And, more serious yet, it has been discovered that another type of non-disjunction leads to mongolism, a type of mental deficiency, accompanied by flattened eyes and rounded face.*

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* Mongolism occurs, on the average, once in every 600 births, but the incidence rises steeply to a few per cent of all children born to women who are over forty, hence, a new hazard to late child-bearing.

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Muller, in his Ph.D. thesis in 1916, further analyzed "crossing-over" and suggested several models, still valid today, to explain how the thread-like chromosomes inherited from one parent may break apart virtually anywhere and "cross-over" to combine with the appropriate pieces of chromosomes inherited from the other parent.

From 1910 to 1927, Morgan, Sturtevant, and Bridges (?) kept the "fly room" at Columbia in continuous operation, except for summers when they would ship their flies in barrels up to Woods Hole, Massachusetts, the famous research retreat of biologists. In this period Columbia became as great a magnet for foreign students of biology as the great European laboratories were for American students of physics and chemistry. Morgan, Sturtevant, and Bridges were known irreverently but affectionately as the "holy trinity" and European students fortunate to work under them returned home wearing their own "haloes" of distinction.

In 1928 Morgan was invited to create a department of biology at California Institute of Technology, and Sturtevant and Bridges made the move with him. Largely as a result of their spirit and effort, Caltech has become one of the world's leading centers of genetic research. Bridges died in 1938 and Morgan in 1945. Sturtevant, now sixty-nine, no longer teaches, but he maintains his lab at Caltech and diligently examines a hundred or so fruit flies under his microscope every day, still charting the inexhaustible patterns of heredity.

? or 100 x 100

"Dollar bills on the sidewalk"

Herman Muller, [reluctant to stay in] [ready to emerge from] Morgan's shadow, left Columbia in 1915, the year that saw the publication of one of the great works of modern biology, The Mechanism of Mendelian

Heredity, written jointly by Morgan, Sturtevant, Bridges and Muller. The last three of the authors were not yet twenty-five years old when the book went to press. Muller than began the research, initially with Altenburg at Rice Institute, Texas, later without him at the University of Texas, that led to the production of artificial mutations in fruit flies. Muller succeeded where Morgan and others had failed because he conceived a sensitive experimental method capable of detecting mutations that were lethal, which over 90 per cent of mutations are. The problem is that a certain number of mutations occur spontaneously, induced by the ordinary hazards of the environment, including cosmic rays and other "background" radiation. By using radium, x-rays, or other mutagens -- even heat -- the mutation rate can be raised, but if the search is restricted to survivors, the rate is still low. "It's like looking for dollar bills on the sidewalk," says Muller. His stratagem was to design breeding experiments that would, in the absence of a mutagen, produce a statistically reliable number of each of several types offspring. Then when he subjected adult flies to a mutagen like x-rays, he could show that the expected number of some types of offspring did not appear. This was not because he had induced in fertility in the parents (though this could happen too) but because the embryonic flies never survived to be born. They were the victims of lethal mutations.

Muller published his first evidence in 1927. As a

result of his research, he became one of the first to crusade for sharp restraint in medical use of x-rays, and since Hiroshima he has been among the most vehement critics of atomic bomb testing. (QUOTATION KOMING)

How genetics was killed in Russia

Muller was perhaps the only Western ~~geneticist~~ scientist to witness, at first hand, the demise of [scientific] genetics in Russia. In 1933 he accepted an invitation to work in Moscow at the Institute of Genetics. He was given a better salary than he had received in the U.S., and all the assistants he needed, not to mention a small chauffeur-driven Ford. At the time, the Russians themselves were doing outstanding research and Muller found the environment friendly and stimulating.

He soon learned, however, that a Ukrainian plant-breeder named Lysenko was making a career of denouncing "Mendelist-Morganist" genetics. Lysenko, reviving the discredited Lamarckian view of evolution, and distorting the examination of practical breeders claimed that plants and animals were molded by their environment and that they could transmit externally acquired characteristics to their descendents. He purported to have experimental evidence for this claim, though he was better at flourishing examples of his supposed plant-breeding achievements than in explaining exactly how they were produced. Not surprisingly, Lysenko's doctrine appealed strongly to Soviet politicians, including Stalin himself, because it promised, in

effect, that Soviet Society could mold a new Soviet Man, right down to his genes.

By 1936, the party newspaper Izvestia was hounding leading geneticists out of their jobs and Muller could see that real research in the field was doomed. In 1937, when a number of his friends disappeared, Muller packed up and left. After teaching a while at Edinburgh, he returned to the U.S. and since 1945 has been at Indiana University. When the Soviet Academy of Sciences officially endorsed Lysenkoism in 1948, Muller addressed a sharp letter to the Academy, resigning his old membership, and accusing the leaders of the Academy of "misusing their positions to destroy science for narrow political purposes." Soviet journalists angrily retorted that Muller had "joined forces with racists and reactionaries," that his theories had done "great damage" to Russian agriculture, and, anyway, that he looked like a "Baptist missionary."

Why corn is as high as an elephant's eye

In the view of most biologists the development of genetics is the premier accomplishment of biology in this century. Throughout the Twenties and Thirties the concepts laid down by Morgan and his associates were widely confirmed and extended. While the fruit fly, raised by the tens of millions, remained the primary research animal, a vast amount of genetic study was also given to corn, mice, chickens, and

a few large animals. The corn work, in particular, had great practical consequences for it led to the development of the vigorous hybrid varieties that are now standard in the U.S., and which so impressed Khrushchev last year when he visited Iowa. These hybrid corns can be traced back directly to findings made in 1905-to-1910 by a geneticist of the Carnegie Institution, George Shull. In the late Twenties, Shull's findings were skillfully and profitably applied by Henry Wallace, whose firm was for years the leading supplier of hybrid corn to American farmers.

Sr. + Jr. (?)

Hi Bred Corn

Do you know the whole about priority here?

The development of corn hybrids was merely the latest chapter in the ancient story, going back beyond recorded history, of man's plant-breeding efforts which, step by step, have shaped our civilization. The wonder is that man could achieve so much with nothing but patience and his limited intuition. And even the empirical success of the corn hybrids, though based on scientific research, rested on no far transcended any deep understanding of what genes and chromosomes really were, but rather on the mechanical laws of distribution of genes which happen to give useful characters.

As late as 1926 when Morgan wrote his great summary work, The Theory of the Gene, the definition of a gene was at best an operational one: it was an entity a something or other located in the chromosome that influenced or controlled a ~~single~~ particular physical and observable aspect of a plant or animal -- it might control the color eye or shape of wing in a fruit fly, the color or texture of a kernel of corn, or the shade of a man's skin. Some genes were dominant, others recessive. And, of course, genes could be altered by mutations. But even as late as 1926* there were biologists who argued that while genes -- whatever they were -- might influence superficial aspects of living things, the real, deep down hereditary control was exercised by something in the cell as yet undiscovered, e.g. the undefinable protoplasm. The great problem of gene theorists, therefore, was to identify what a gene really was, physically and chemically, and to show how it exercised its all-pervasive control -- if, indeed, its control was all-pervasive. To be sure, there was no lack

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of hypotheses, and a few of them were remarkably prophetic.

As early as 1908 an Oxford physician and biochemist named Sir Archibald E. Garrod, proposed the concept of "inborn errors of metabolism." By this he meant that a plant or animal might be born lacking one or more enzymes (chemical catalysts) needed to perform a certain job of all chemistry. One such "inborn error" cited by Garrod was the human defect known as alcaptonuria, whose chief symptom is the blackening of urine on exposure to air. The urine blackens because it contains a certain organic acid. Garrod reasoned that normal individuals must possess a specific enzyme for destroying this acid and that the enzyme must be missing in alcaptonurics. He suggested further that absence of this enzyme was associated with a recessive gene; when a person inherited two such recessives, alcaptonuria resulted. Garrod's ideas were
23 little attended.

In 1917, Sewall Wright, the brilliant geneticist now at the University of Wisconsin, made an equally bold effort to draw genetics and biochemistry together. He proposed that the pigment, melanin, that produces the skin coloration in men and animals, is the result of a series of enzyme reactions under genetic control. He concluded that "By constant comparison of the deductions /of the geneticist/ with the findings of the biochemist, it should be possible in the end to establish a very pretty correlation of results."

Like Garrod's suggestions, Wright's too lay fallow. The time was not ripe for pretty correlations. There was no hint of a pathway to link a gene of unknown shape, size, or chemistry, with an enzyme of equally unknown nature. It was not until 1926 that James B. Sumner isolated the first enzyme in crystalline form and showed it to be a pure protein, i.e., a long-chain macromolecule made up of simple subunits called amino acids. Slowly it became clear that the countless types of proteins produced by the cell -- many of them enzymes to catalyze the chemical activities of the cell, others the proteins needed for cell walls, for skin and muscle and sinew and blood and hormones and hair and nails -- are all composed of unique macromolecules, each with its own characteristic composition and arrangement of amino acids. In the last ten years, vast strides have been made in establishing the precise structure of a number of simple proteins, a topic to which we shall return.

The lesson of the hungry bacteria

But what is a gene? and how does it indeed direct the synthesis of enzymes and other proteins? The man who did the 24 most to connect gene and enzyme is George W. Beadle, fifty-six, who succeeded Thomas Hunt Morgan as head of biology at Caltech. Hearty and friendly, Beadle is quite unlike the stereotype of the scientist, but his appearance is deceptive. Friends know

him as one of the most industrious workers who ever entered a laboratory, and his brilliant concepts have been crucial in transforming biology into a more unified science than ever before.

Beadle was born on a farm in Wahoo, Nebraska, where he learned the pioneer virtues of thrift and hard work. His exposure to science was nil until he reached high school, when he developed a boyish crush on an attractive young teacher of physics and chemistry. She urged him to attend college despite his father's view that he had had enough schooling. In 1922 he entered the University of Nebraska's College of Agriculture, intending ultimately to become a farmer.

At the college he was drawn to genetics by a professor who was experimenting with hybrid wheat. Beadle stayed on for a master's degree and then earned an assistantship at Cornell, where he came under the influence of Rollins A. Emerson, one of the pioneers in the genetics of corn. Beadle's Ph.D. in 1931 combined cytology and genetics. With a National Research Council Fellowship, he then moved on to Caltech where he learned about fruit flies from a master, A. H. Sturtevant.

After three years at Caltech, Beadle began to feel that corn and fruit-fly genetics were not really coming to grips with the way genes influenced cell development and growth. Taking a leave, he went to the University of Paris in 1935 to

work with a young embryologist, Boris Ephrussi. Their research objective: to transplant an eye from one fruit fly larva to another to see whether the transplanted eye would change color under the influence of chemicals in the new host. The work was difficult and frustrating, but it lead Beadle and Ephrussi to formulate, in somewhat vague fashion, the hypothesis that each gene might control one specific enzyme. But this still remained to be shown. Beadle returned to the U.S. and continued the eye color studies at Stanford where he was appointed a full professor in 1937. There he was joined by a top flight young chemist, Edward L. Tatum, whose task was to identify the color-forming compounds.

By 1940 Beadle and Tatum saw that they were getting bogged down in complexities and might never be able to show a clear connection between gene and enzyme. What they needed, they recognized, was a biological system much easier to manipulate, in which they could force nature to give unequivocal answers. The notion was just then gaining currency that microorganisms like bacteria and molds, far from being simple, actually possessed chemical powers far surpassing those of fruit flies, mice, or even men. The basis for this new idea was that microorganisms could live on very simple cultures containing none of the vitamins and amino acids required by higher organisms. It was not that the little bugs could do without these substances, but that they were able to manufacture them internally

from very simple nutrients.

This gave Beadle and Tatum the inspired idea to turn their attention to the ~~pink~~ red bread mold known as Neurospora crassa, a microorganism which, they quickly found, can thrive on a simple culture consisting only of a few inorganic salts and sugar, spiked with a vitamin called biotin. They reasoned that Neurospora must contain all the enzymes needed to make other vitamins and amino acids, and that these enzymes must be controlled by genes. If so, exposing Neurospora to X-rays should cause some of the genes to mutate, thereby knocking out some of the enzymes. Result: a Neurospora that needed vitamin or amino acid supplements to live. "There was no doubt in our minds that we would find the mutants we wanted," Beadle has recalled; "We had only one worry -- that their frequency might be so low that we would get discouraged and give up before finding one."

The worry was unfounded. The 299th spore, or reproductive cell, which they irradiated gave a mutant strain requiring vitamin B_6. The 1090th spore required vitamin B_1. Before long they had produced dozens of mutants, all unable to make some essential compound that the "wild" or normal strain of Neurospora makes without effort. The goal that Beadle had sought unsuccessfully with fruit flies for over five years was suddenly reached almost overnight. In 1941 Beadle and Tatum published their dramatic evidence that the way genes work is by controlling

the production of enzymes and, through the enzymes, the fundamental chemistry of the cell.

The riddle of the changeable pneumococcus

The stage was now set for what some biologists regard as the greatest genetic discovery of the century. Like many of the great experiments in science, it showed that what everyone believed to be so was not so. The gene, a vaguely-defined "factor" when Morgan began his experiments, had slowly materialized over the years into a tangible chemical substance located in the chromosomes. But what was the chemical substance? Everyone assumed that the essential part of the substance was a protein. The fact that chemical analysis showed chromosomes to consist of an intimate mixture of proteins and a substance called nucleic acid was dismissed as interesting but irrelevant.

Around 1940 (CK), Oswald T. Avery, a Rockefeller Institute research physician, close to the age when many men are thinking of retirement (he was sixty-two), believed he saw a clue to the nature of the gene in a curious finding reported in 1928 by an Englishman, F. Griffith. He had injected mice with two different strains of pneumococcus bacteria: one strain living, but harmless, called "R," the other strain killed by heat before inoculation, but which would have been fatal to mice had it not been killed. The virulent (but now

dead) strain was called "S." There was another equally important difference between the two strains of bacteria: the virulent strain, "S," had a distinguishing capsule structure encasing each bacterium which the harmless strain "R" lacked. The expected result was that mice so injected would survive. Instead, some died. To his astonishment, Griffith found that the blood of the dead animals contained thriving and virulent bacteria of type "S," complete with capsule. One of two things must have happened: either the dead "S" bacteria had miraculously been brought back to life, or else the "R" bacteria had been transformed, almost as miraculously, into "S" type.

Griffith and others, who repeated his work, could show that the lesser "miracle" had happened: "R" had been transformed into "S." Since bacteria are such tiny creatures, the transformation may not sound very dramatic, but were it to take place in a creature as large as a dog, it would be like changing a line of ~~pekinese~~ hairless Chihuahua into St. Bernards. Indeed, a few geneticists had suggested that transformation was akin to performing a controlled mutation. But no one could explain just how the transformation took place.

This was the question that Avery tackled afresh with the help of two young colleagues, Colin M. Macleod and Maclyn McCarty. The difficult and often frustrating task took them HOW LONG (four years?) and Avery was sixty-seven when the work was finally published in 1944. The three men grew pneumococcus "S" bacteria in batches of seventy-five gallons or more and, by one strategem after another, finally sifted out the "transforming principle" -- the mysterious substance that would transform "R" bacteria into "S." From seventy-five gallon batches of broth they were able to isolate less than a thousandth of an ounce of the "principle," a sticky material that could be wound in fibrous strands around a glass stirring rod. For the first time in history man could see genes, naked and unalloyed. 25

Avery, properly conservative, was not so bold as to say he had isolated genes. But his paper spoke for itself.

proper, yr

When this sticky material was added to pure cultures of "R" bacteria, it evidently penetrated some of the "R" cells and there introduced the genetic instructions needed to transform "R" cells into "S" cells. Avery found that the "transforming principle" was a long-chain polymer of high molecular weight and that it was not a protein. He showed, instead, that it was the neglected nudeic acid, or more properly, deoxyribonucleic acid, now famous as DNA. Biologists were dumbstruck.

In the long view of history, Avery's work may rank with the immortal discoveries of all time. Yet he failed to win a Nobel Prize, perhaps because he died in YEAR, before the Swedish Academy could bring itself to act, and he is not even listed in the latest edition of the Encyclopedia Britannica.* What about Griffith?

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* By contrast, Luther Burbank (1849-1926), who was the Thomas Edison of plant breeding, is allotted fifty-six lines of space, fourteen more than Thomas Hunt Morgan.

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A physicist's approach to biology

While geneticists were still puzzling over the significance of Avery's work, many of them reluctant to concede its deep significance, a dramatic confluence of discoveries con-

firmed the genetic role of DNA and ultimately transformed biology at its foundations. For this new research, the fruit fly, as Beadle and Tatum had shown, was enormously too large, too complex, and too slow in breeding. The organisms that were to carry biologists into the new realm were the bacteria of Beadle, Tatum, and Avery, and a still smaller molecular "apparatus" -- the viruses, especially the viruses known as bacteriophages, or simply as phages, that infect bacteria. The phages, and their complaisant hosts, have been to biology what the huge atom smashers have been to physics: they have permitted biologists to "See" finer and finer details of their primary structural entity, the gene.

To raise a million fruit flies, and trace their heredity in detail, can absorb a geneticist for a lifetime. A million bacteria can be grown to visible dimensions in a glass petrie dish overnight. And, using the nutritional-requirement techniques of Bendle and Tatum, it is no trick at all to spot a single mutant among a million, or even a billion cells. When phage are combined with bacteria the generations multiply faster yet. In a dozen minutes a single phage particle can enter a bacteria cell, take over command of the cell's chemical machinery, and construct a hundred or more replicas of itself, which pour out of the cell in a search for new victims.

In the fifteen years since the close of World War II

new findings in bacterial and phage genetics have piled up so fast that fruit-fly geneticists, the "classicists" in the business, are lost and bewildered. The new "heretics" have adopted the communication schemes long familiar in physics: they bombard each other with letters and "preprints" of their latest results, and they tirelessly visit each other's laboratories.

The two men who had the most to do with binding the "heretics" together, are Max Delbrück, of Caltech, and Salvador Luria of M.I.T. Delbrück, fifty-three, is a theoretical physicist, born and educated in Germany, who began turning his interest to biology in the early thirties while still the chief theoretical physicist at the Kaiser Wilhelm Institute in Berlin. As a young post-doctoral student under the great Niels Bohr in Copenhagen, Delbrück had been exposed to Bohr's concept of "complementarity," a philosophical concept adduced to explain how atomic particles can show the properties of both particles and waves. (See the first article in this series, March, 1960.) Delbrück began speculating whether biologists would ultimately encounter similar paradoxes as they probed deeper and deeper. Impatient to learn the answer, he switched over to biology.

Delbrück came to the U.S. in YEAR and obtained a position at Vanderbilt University, in Tennessee, where he met Salvador Luria, recently arrived from Italy. Luria, though

trained in biology (medicine then radiobiology + microbiology), shared Delbrück's sharply analytical approach to problems, and the two became fast friends. At Vanderbilt, in the uneasy role of enemy aliens during World War II, they devised important new methods for using phages in genetic research. (NEED A FEW SENTENCES SETTING FORTH THE STATUS OF PHAGE RESEARCH WHEN THEY ENTERED THE FIELD, AND TWO OR THREE OF THEIR KEY CONTRIBUTIONS.) In 1947, Delbrück was invited to Caltech, while Luria went to Indiana University. Since 1959, Luria has been on the faculty of M.I.T. Their students, oriented to physical methods, are at the forefront of the new heretical genetics.

cf. Sir Mac Farlane Burnet – "Virus as Organism" check c/ Hershey.

The Waring blendor experiment

The work of Delbrück, Luria, [and] others, especially a strong group in Paris under NAME KOMING, led, around 1950, to the view that a typical phage particle consisted of a few genes -- ~~presumably~~ possibly macromolecules of DNA -- wrapped up in a protein "overcoat." (CHRONOLOGY OF THIS VIEW NEEDS CHECKING.) The "overcoat" served not only as a package, but it, or sometimes a "tail" appended to it, evidently contained the enzyme needed to eat a hole in the wall of bacterial cells so that the phage's DNA core could enter and do its dirty work.

+ Hershey. Paris contributions to phage work later } Lwoff Jacob Wollman

This hypothesis offered a crucial test of the genetic role of DNA. Many biologists, still doubting that DNA alone could carry genetic instructions, argued that some of the pro-

teins of the phage also entered the cell and participated in the cell's destruction. A beautifully simple test of the rival hypothesis was conceived by Alfred Hershey, a ~~mathematician(??)~~ bacteriologist turned virologist, on the staff of the Carnegie Institution at Cold Spring Harbor, Long Island. (CAN WE TRACE ANY DELBRUCK-LURIA INFLUENCE TO HERSHEY?)

Hershey, and an associate, NAME Martha Chase, devised a way to put a distinctive radioactive label on the protein "overcoat" and "tail" of a phage known as T-2 and a different radioactive label on the DNA enclosed in the "overcoat." Then they let the doubly-labeled T-2 go to work on ordinary bacteria. After a few minutes (CHK), they put the entire mixture in a Waring Blendor, which knocked the T-2 "tails" and "overcoats" loose from the cell walls. With a centrifuge, Hershey and Chase next separated the infected cells, with the T-2 DNA inside, from the protein "tails" and "overcoats." Radioactivity assay of the two fractions showed that none of the labeled protein had penetrated the walls of the bacterial cells. The only radioactivity inside the cells was of the type incorporated in the DNA.

About the same time that Hershey and Chase announced these results, in 1952, Alfred Mirsky, a distinguished biochemist at Rockefeller Institute, was settling another controversial aspect of the DNA story. If DNA was indeed the stuff of genes, every cell in a given organism, be it taken

from liver, heart, skin, or brain -- should contain an identical weight or charge of DNA. This followed from the well-established fact that every cell of an individual has the same genetic inheritance as every other cell. Some biologists held that the DNA content varied from cell to cell, hence that DNA could not act as genes. Mirsky proved that the DNA charge was identical, and the synonymity of genes and DNA was advanced another giant step.

DNA: molecule with a "zipper"

Meanwhile, x-ray crystallographers, whose specialty is inferring the detailed atomic architecture of crystals -- including organic molecules with regular repeating structures -- had been busy studying DNA. Chemists had shown that DNA is built up of thousands of repeating units of a simple sugar (known as deoxyribose), phosphate units, and finally four nitrogen-containing compounds called adenine, thymine, cytosine, and guanine. But how all these sub units were strung together was a profound puzzle. As we shall see, the four nitrogen compounds, hereafter abbreviated, A, T, C, G, turned out to be the most fateful substances in existence. One day they will be as familiar to school children as oxygen, carbon, iron, and uranium, and strontium are today.

Among the leaders in the x-ray study of DNA were Linus Pauling at Caltech (see "The Chemists," FORTUNE, April, 1960), and M. H. F. Wilkins at King's College, London. A number of structural models for DNA were put forward, includ-

ing one by Pauling and R. B. Corey, but they failed to carry much conviction. Then early in 1953, the British journal Nature carried a brand new proposal signed by two men of whom few biologists had ever heard, J. D. Watson and F. H. C. Crick. Pauling and other experts saw immediately that the new model had the simplicity and elegance that frequently bespeaks a correct solution. The Watson-Crick model (actually built as a six-foot model at the Cavendish laboratory, in Cambridge), depicted a helix consisting of two intertwined molecular chains. Tying the two chains together, like rungs on a ladder, were the compounds A, T, C, and G. Each rung consisted either of A linked to T or C linked to G. Watson and Crick calculated that the geometry of the structures forbade other combinations. (Chemists had already discovered, and puzzled over the fact, made more impelling by growing accuracy of analyses, that DNA samples always contained exactly as much A as T, and viz. one of the premises on which it was constructed exactly as much C as G, just as the new model prescribed.)

This invariant pairing, A with T and C with G, provided the most beautiful and compelling feature of the new model. The pairing implied that if the DNA molecule were "unzippered" or split longitudinally down the middle -- separating A's from T's and C's from G's -- each half could serve as a template for recreating the missing half. The model thus suggested for the first time an explicit scheme whereby genes might replicate. If the twin-chained DNA came "unzippered" in the nucleus of the cell, each half of the

molecule could add the A's, T's, C's, and G's needed to fabricate a new half, thereby creating two duplex molecules of DNA where there had been only one before.

The four letter language of life

What is the role of A, T, C, and G, and why four substances instead of just two or some other number? Evidently, A, T, C, and G are the "code letters" which, rearranged endlessly, specify uniquely every organism that ever lived. By using four "letters" nature can pack ~~four times more~~ twice information in a given length of DNA than if it used only two "letters." One may conjecture, further, that penalties -- perhaps in the form of errors -- would enter if the cell had to fabricate and manipulate more than four "letters." A certain number of "letters," perhaps a few thousand, are needed to encode the information contained in a single gene, (i.e., the information needed to specify a single enzyme or other protein). Assuming a bacterium must manufacture a thousand different enzymes, it must have a DNA code some five million "letters" long. Man, at a conservative estimate, is perhaps a thousand times more complex than a bacterium, hence the DNA "message" needed to specify him may be around five billion "letters" long. Written in ordinary type a "message" this length would fill a thousand large volumes. This is the awesome "message" that evolution has been writing at the rate of two or three "letters"

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a year since life began two billion years ago. Even compressed into the tiny molecular "letters" of A, T. C, and G, the genetic message of man would require a DNA molecule (s) total length about five feet long (CK) when fully strung out. There is every reason to believe that man's forty-six chromosomes may actually contain, tightly coiled and involuted, something like this much DNA.

The scientists who conceived the 1953 model of DNA, since confirmed by numerous experiments, are a thirty-two-year-old American, now a professor of biology at Harvard, James Dewey Watson, and a WHAT-AGE Englishman, Francis H. C. Crick, who is a physicist-turned-biologist at Cambridge University. Since 1953 both have amply proved themselves to be among the most gifted young scientists in their two countries. Watson, an avid bird watcher as a boy, earned his Ph.D. in biology at Indiana, where he studied under Muller and had Luria as his thesis professor. As Muller had been deeply influenced by a book in 1908, Watson was similarly influenced -- as were many of his age -- by a provocative book called What is Life? based on lectures delivered in Dublin during World War II by the great Austrian physicist, Erwin Schrödinger.

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Following his Ph.D. in 1950, Watson spent two years in Copenhagen and then, at Luria's urging, went to Cambridge where he met Crick. (Luria helped arrange the Cambridge trip by making two phone calls (TO WHOM, WHERE), "The most fruitful phone calls I ever made in my life," says Luria.) At the

present time, Watson and Crick, working independently, are trying to crack the code by which DNA instructs the cell how to construct the thousands of different kinds of proteins -- each unique and with its own specific job -- needed by a living organism.

This "coding problem," as it is called, is absorbing many of the keenest minds in biology, biochemistry, and physics. The problem, in brief, is this. DNA, limited to a "language" of four "letters," must somehow tell the cell how to assemble proteins which contain a "language" composed of twenty "letters" -- the twenty different amino acids which, strung together in chains of dozens, hundreds, and even thousands of units long, constitute the various proteins. Presumably, some sequence of A's, T's, C's and G's, in DNA, specify a unique sequence of amino acids in a protein. According to this view, a mutation which alters a short stretch of the DNA code -- conceivably even a single "letter" -- will cause a change in at least one amino acid in the chain of a protein. How significant a change in just one amino acid, among hundreds, can be has recently been discovered in a study of the blood protein, hemoglobin. At M.I.T., * Vernon M. ~~FIRST NAME~~ Ingraham has shown that the human disease known as sickle-cell anemia is caused when one amino acid valine ~~(NAME KOMING)~~ is substituted for the normal one glutamic acid ~~(NAME KOMING)~~ at one specific point in a molecule containing several hundred amino acid-units.

Verne?

* did this work at Cambridge in Crick's unit.

DNA: new copies by the quadrillions

The most brilliant biochemical achievement yet to be carried out on DNA has been its successful replication outside a living cell. The feat was performed in 1957 by Arthur Kornberg, then working at Washington University, St. Louis. The accomplishment is the latest triumph in a story extending back to 1828 when Friedrich Wöhler confounded the "vitalists" of his day by producing urea in a test tube. (Previously urea, and other "organic" compounds, had been regarded as an exclusive product of living organisms, not to be duplicated by man.)

Kornberg, a forty-two-year-old M.D. turned biochemist, set himself the formidable task soon after the Watson Crick model of DNA was published. "My point of view," he says, "is that there is no stopping anyplace. We must cease marveling at the cell. The chemistry it performs can be understood and duplicated. Of course, if you don't succeed, you've been foolish. If you do succeed, you're called great." Kornberg had previously worked out the cell's scheme for making the four "letters" of DNA, A, T, C, and G. He made the bold assumption that if he put these "letters" in a test tube along with the other constituents of DNA and then added a little natural DNA to serve as a primer, he could ultimately create the conditions needed for further replication. But what were these conditions? He assumed from the start that he would have to isolate some sort of x-factor from the nucleus of living cells

which would promote replication. After months of patient search and hundreds of failures, he and his associates isolated an enzyme which, when added to the test-tube mixture, created tiny traces of new DNA. They could be sure it was newly-formed because the ingredients carried radioactive tags, and the DNA primer was untagged. (The DNA primer may be obtained from plants, animals, bacteria, or viruses; the source is immaterial.) Kornberg called the enzyme "polymerase," indicating that it promotes polymerization. Ultimately, with purified polymerase, Kornberg has been able to produce twenty times as much new DNA as that used as primer, and the reaction is so fast that a billion billion molecules of DNA can be created in a few minutes. Each of the billion billion molecules contains roughly 10,000 sub units of A, T, C, and G, which have to be plucked out of the crude mixture (assisted by polymerase) and fitted precisely into the right place in the DNA molecule. While there is no analytical method known that will guarantee that the DNA has been replicated exactly, there is a good preliminary evidence in favor no reason to assume otherwise. The crucial test of this assumption, not yet achieved, would be to show that the synthetic DNA has precisely the same biological activity as the DNA primer. Kornberg has no doubt that such activity will ultimately be shown. Meanwhile, at Stanford University Medical School, where he now teaches, he is trying to purify and crystallize polymerase, hoping eventually to establish its precise

amino-acid sequence and structure.*

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* The British have been the world leaders in protein research. Frederick Sanger of England won the Nobel Prize in 1958 for establishing the precise sequence of the fifty-one amino acid units that link together to form the protein insulin. Within the past year, British x-ray crystallographers have published the complex three-dimensional structures of hemoglobin and a similar muscle protein called myoglobin. These twisted and folded proteins each contain a few hundred amino acid units, and their complete sequence has not yet been determined. Such studies bear directly on the "coding problem." No one knows yet whether DNA simply has to specify the amino-acid sequence of a protein, leaving the three-dimensional twisting and folding to take place spontaneously, or whether the DNA has to provide complete folding instructions as well.

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The curious sex life of bacteria

Perhaps the characteristic that most surely marks a vigorous, fast-moving science is its ability to produce brilliant young leaders. The first upsurge of genetics produced Muller, Sturtevant, and Bridges, all of whom did distinguished work before they were twenty-five. Since World War II, American biology has produced a young man, now thirty-five, whose career

suffers nothing in comparison with these earlier giants. His name is Joshua Lederberg.

At twenty-one, working at Yale with his teacher Edward Tatum, he discovered that bacteria, long believed to reproduce only asexually, sometimes employed (if not enjoyed) sexual reproduction. Lederberg and Tatum found that two bacterial cells will sometimes come together in temporary union and genetic material will pass from one cell to the other. As in the world of larger organisms, this genetic exchange confers on bacteria increased flexibility in adapting to their environment.

When Lederberg was twenty-seven and teaching at Wisconsin, he and one of his own students, Norton D. Zinder, discovered what may be the most bizarre scheme of all for transfer of genetic information. The scheme was so difficult to unravel that trillions of bacterial cells had to be carefully followed in hundreds of experiments. The upshot was that certain phages "living" in peaceful symbiosis inside bacteria sometimes "steal" a single gene from the host and carry it outside the cell. The phage may then penetrate another cell and present it with the stolen gene. At this point a "choice" is made, and the bacterium may "substitute" the foreign gene for one of its own, passing it along to its daughters. Lederberg and Zinder named this exotic process transduction. (WILL LEDERBERG HELP US FRAME A SENSIBLE SENTENCE OR TWO SUGGESTING

WHAT ROLE, IF ANY, TRANSDUCTION MAY PLAY IN HUMAN DISEASE? PERHAPS EVEN IN CANCER?)

Lederberg shared the 1958 Nobel Prize in medicine and physiology with Beadle and Tatum. He is now teaching at Stanford University medical school, where one of his close research associates is his wife Esther. 31

Trained in classical biology, Lederberg concedes that he once held strong reservations about the role that the heretics were assigning to DNA. "Biologists have been schizophrenic on the matter of 'vitalism,'" he said recently. "Virtually all of them are avowedly mechanistic, but at the same time they have been reluctant to believe they could really understand the deep problems of biology. They have been so impressed with the diversity of life that they are suspicious of simple answers. The molecular explanation offered by DNA was extremely offensive to them. I can remember clearly when my own thinking changed. I came to realize that it may be more constructive not to insist on absolute verification. The Watson-Crick structure and its model for replication really ~~is~~ was based on inadequate evidence. But it may be more fruitful to advance as rapidly as we can. Science always oscillates between periods of rapid advance and periods of consolidation. Biology is now in the fast and sloppy stage. Trying to foresee all the implications of pure exact chemical studies. But I am convinced that with DNA and other molecular concepts we will find answers even to problems of great subtlety."

The new "dogma"

Young biologists jokingly refer to the sweeping view that DNA controls all as the current "dogma." No one has pushed the dogma further and deeper than thirty-eight-year-old Seymour Benzer, who received his Ph. D. in physics in 1947. Another to come under the spell of Schrödinger's What is Life?, Benzer asked Purdue, where he was an instructor, for a year's leave to look into biology. He stretched the year to four and returned fired with the new "religion" of DNA and viruses preached by Luria, Delbrück, and Hershey. 30

Back at Purdue, Benzer conceived the idea of mapping the "chromosomes" of phage viruses as Sturtevant had earlier mapped those of fruit flies. "My goal," he says, "was to run the map into the ground." By raising trillions of viruses and noting how they mutated, he has been able to draw maps with a wholly new order of ultrafine detail. He has thereby shown that a change affecting just one or two "letters" in the A-T-C-G code of DNA will produce a discernible change in the habits of a virus. By contrast, he has found that the functional unit normally described as a "gene" may consist of a few thousand "letters." To sharpen genetic discussion, Benzer has coined and defined new terms like "muton," "recon," and "cistron." Geneticists are indebted to him for throwing a sharp light in a murky area.

One of the great problems for the future is to show

how DNA molecules are fitted into the chromosomes, which in plants and animals are so large that they are readily visible under an ordinary microscope.[33] Every scheme so far proposed for packing the tiny threads of DNA into these much larger structures runs into formidable obstacles. The problem is that DNA, no matter how tightly twisted and coiled, must be free to "unzipper," to replicate, and yield two molecules that can pull cleanly apart. Once again human intuition is frustrated by biology's incredible detail.

There is yet no sign that the sixty-year drive that has carried genetics down to the level of molecular dimensions has slackened its pace. The danger is ever present, of course, that current ideas may be profoundly wrong.[32] The glory of science, however, is not that it discovers "truth" but rather that it advances inexorably by discovering and correcting error. The scientist's view of the world is always subject to change without notice, but the intricate edifice of verifiable fact and tested theory that has been patiently created in just a brief few hundred years is man's most solid achievement on earth.

(END)